Inflammation-driven deaminase deregulation fuels human pre-leukemia stem cell evolution.

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Public Summary:
Inflammation-dependent base deaminases promote therapeutic resistance in many malignancies. However, their roles in human pre-leukemia stem cell (pre-LSC) evolution to acute myeloid leukemia stem cells (LSCs) had not been elucidated. Comparative whole-genome and whole-transcriptome sequencing analyses of FACS-purified pre-LSCs from myeloproliferative neoplasm (MPN) patients reveal APOBEC3C upregulation, an increased C-to-T mutational burden, and hematopoietic stem and progenitor cell (HSPC) proliferation during progression, which can be recapitulated by lentiviral APOBEC3C overexpression. In pre-LSCs, inflammatory splice isoform overexpression coincides with APOBEC3C upregulation and ADAR1p150-induced A-to-I RNA hyper-editing. Pre-LSC evolution to LSCs is marked by STAT3 editing, STAT3beta isoform switching, elevated phospho-STAT3, and increased ADAR1p150 expression, which can be prevented by JAK2/STAT3 inhibition with ruxolitinib or fedratinib or lentiviral ADAR1 shRNA knockdown. Conversely, lentiviral ADAR1p150 expression enhances pre-LSC replating and STAT3 splice isoform switching. Thus, pre-LSC evolution to LSCs is fueled by primate-specific APOBEC3C-induced pre-LSC proliferation and ADAR1-mediated splicing deregulation.

Scientific Abstract:
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